Characteristics of sudden death in hemodialysis patients

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Hemodialysis (HD) is an intermittent procedure during which large fluid and electrolyte shifts occur. We hypothesized that sudden death occurrences in HD patients are related to the timing of HD, and that they occur more frequently in the 12 h period starting with dialysis and in the 12 h period at the end of the dialysis-free weekend interval. In a retrospective study, 228 patient deaths were screened to determine if they met the criteria for sudden death. Information was obtained from clinic charts, dialysis center records, and interview of witnesses of the death event. There were 80 HD patients who met the criteria for sudden death. A bimodal distribution of death occurrences was present, with a 1.7-fold increased death risk occurring in the 12 h period starting with the dialysis procedure and a threefold increased risk of death in the 12 h before HD at the end of the weekend interval ($P = 0.011$). Patients with sudden death had a high prevalence of congestive heart failure and coronary artery disease. Only 40% of patients experiencing sudden death were receiving beta-blockers, and the prior monthly serum potassium value was less than 4 mEq/l in 25%. Sudden death is temporally related to the HD procedure. Every other day HD could be beneficial in preventing sudden death. Careful attention to the usage of beta-blockers and to the maintenance of normal serum potassium values is indicated in HD patients at risk for sudden death.

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Cardiovascular disease is accelerated in end-stage kidney disease patients and is responsible for much of the increased mortality observed in hemodialysis (HD) patients. The incidence of cardiac arrest or cardiac arrhythmia was 62/1000 patient years at risk for all US dialysis patients between 1999 and 2001, accounting for 26% of all deaths. The incidence was 93.7/1000 patient years at risk for dialysis patients greater than 65 years of age.[1] This incidence is almost twice than that found in the year following myocardial infarction in a group of patients from the general population with coronary artery disease (CAD) (approximately 51 deaths/1000 patient years).[2] The high rate of sudden death in the dialysis population may not only be related to the high prevalence of underlying cardiac disease but also the stress of the HD procedure itself. The purpose of the present study was to determine the timing and characteristics of sudden death in a population of dialysis patients. A previous study showed an increased rate of sudden death on Mondays for Monday, Wednesday, and Friday HD patients and Tuesdays for Tuesday, Thursday, and Saturday HD patients.[3] However, this study was unable to determine the exact timing of sudden death (i.e. if deaths occurred in the hours before or after dialysis). In addition, previous studies have involved large databases and not been able to examine each individual death and apply a strict definition of sudden death. The rationale for this study was that detailed analysis of sudden death events and patients sustaining them would provide a better characterization of this common event and provide insights into potential methods of prevention.

HD is typically performed on Monday, Wednesday, and Friday, or Tuesday, Thursday, and Saturday for the vast majority of dialysis patients. This timing results in two 48 h and one 72 h interval between the start of dialysis treatments (see Figure 1). We hypothesized that sudden death events were more likely to occur in the 12 h interval beginning with the start of dialysis and in the last 12 h interval (occurring 60–72 h after dialysis) that occurs once a week at the end of the weekend dialysis-free interval as compared to the 12–60 h interval.

RESULTS

Of 228 deaths reviewed, 88 (39%) met the criteria for sudden death. On the End-Stage Renal Disease Death Notification

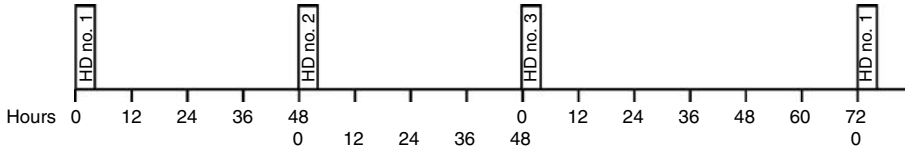

Figure 1 | Timing of HD sessions.

Form (Form HCFA 2746-U3), the patient's primary nephrologist classified 59 (67%) of these deaths as cardiac arrest, cause unknown, six as acute myocardial infarction, four atherosclerotic heart disease, three cardiomyopathy, two pulmonary edema, two 'other', one valvular heart disease, and 11 unknown. Of the 140 deaths that did not meet the criteria for sudden death, 13 (9.3%) were classified as cardiac arrest cause unknown. Eight of the patients who suffered from sudden death were patients undergoing peritoneal dialysis and were excluded from the rest of the analysis. Of the 80 sudden deaths, 51 (64%) were witnessed. There was a $\leqslant 2$ h interval for 11 patients (14%), 2–5 h for eight patients (10%), and 8–12 h for eight patients (10%). For one patient, the hour of death could not be determined accurately. For one patient, the timing of the last dialysis could not be determined.

Figure 2 shows the ratio of observed to expected death proportions for each 12 h time interval, assuming an equal temporal distribution of death. The observed to expected death rates overall were significantly different than expected ($P = 0.0008$). There were 28.5 deaths in the first 12 h period compared to the expected 16.6 deaths (1.71 ratio observed to expected, $P = 0.036$). Of these deaths, 12/28.5 (42.1%) occurred during the dialysis procedure. For the rest of the interval, there were 16.5 deaths vs the expected 11.1 deaths (1.49 ratio observed to expected, $P = 0.10$). After the first 12 h period, the death occurrences decreased dramatically and then began to increase at the 48–60 h interval. This interval occurs on Sunday morning for Monday, Wednesday, and Friday HD patients, and represents the time the patient would return for dialysis if dialysis was performed every other day and there was no weekend interval. In the 60–72 h time period, there were three times as many observed deaths as expected (16.5 vs 5.5 expected, $P = 0.011$).

Of the 29 deaths occurring in the 12 h period beginning with the dialysis treatment (0–12 h interval), nine (31%) occurred following the dialysis treatment after the weekend interval – that is, on Monday or Tuesday vs the 33% expected ($P =$ NS).

Table 1 shows the characteristics of patients who suffered sudden death. A large proportion of the patients suffered from CAD, other vascular disease, congestive heart failure (CHF), or diabetes mellitus. CHF or CAD was present in 57 of 80 patients (71%).

Echocardiograms were performed in 69 individuals who ultimately suffered sudden death. The mean time interval from the time of the echocardiogram until death was 9.8 ± 12 months. Results from these echocardiograms and prior electrocardiograms are shown in Table 1. Electrocardiographic findings revealed left bundle branch block in 9% of patients, atrial fibrillation/flutter in 9.0%, and a paced rhythm in 3.9%. A prolonged corrected QT interval (>0.44 s) was present in 53.5% of patients.

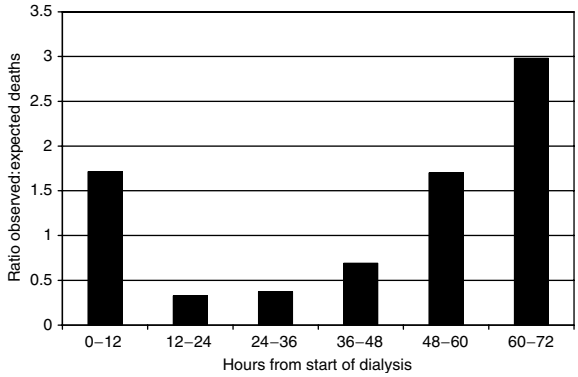

Figure 2 | Ratio of actual to expected number of occurrences of sudden death for each 12 h interval beginning with the start of HD.

Nineteen of the 77 patients (24.7%) with prior monthly laboratory studies had a serum potassium value less than 4 mEq/l. In the previous month, nine (47%) of these patients had a serum potassium value less than 4 mEq/l. In all, 27% of patients had a serum albumin <3 g/dl in the previous month, 50% had a hemoglobin <11 g/dl, and the serum phosphorus was greater than 6.5 mg/dl in 36% patients.

Only 32 of 80 (40.0%) patients were receiving a beta-blocker. Only 9/32 (28.1%) patients with a left ventricular ejection fraction $<50\%$ were receiving beta-blockers. Of 45 patients with CAD, 19 (42.2%) were receiving a beta-blocker. Of 24 patients receiving dihydropyridine calcium channel blockers, 15 (63%) were receiving beta-blockers. Characteristics of the final HD treatment are presented in Table 2.

Characteristics of individuals who died in the 0–12 h interval are compared to those who died in the 12–60 h period and the 60–72 h period in Table 3. There was a trend for patients who died in the 0–12 h interval to have an increased incidence of CHF, CAD, and stroke. In contrast, the individuals who died in the 60–72 h interval had a lower incidence of these conditions, although not statistically significant. The serum potassium of individuals in the 60–72 h interval tended to be higher than that of individuals in the 0–12 h interval. Patients who died in the 60–72 h were more likely to be on beta-blockers (58.8%) than individuals who died in the 0–12 h interval (31%) or the 12–60 h interval (37.5%) ($P = 0.01$).

Table 1 | Patient characteristics

Characteristic	Mean ± s.d. or *n* (%)
Age (years)	60.3 ± 14.1
Female	47 (58.8%)
African-American	43 (53.8%)
Vintage (years on dialysis before event)	3.53 ± 3.6
Hypertension	74 (92.5%)
History of seizures	8 (10.3%)
Significant non-compliance	17 (21.3%)
Tobacco usage	41 (51.3%)
Diabetes mellitus	46 (57.5%)
Coronary artery disease	45 (56.3%)
Congestive heart failure	44 (55.0%)
Echocardiographic findings	
LVEF	46.6 ± 16.9
⩽35%	17 (24.6%)
35 to <50%	15 (21.7%)
50 to <60%	26 (37.7%)
>60%	11 (15.9%)
Segmental wall motion abnormalities	33 (47.8%)
Electrocardiographic findings	
Rate (b.p.m.)	84.6 ± 17.9
QT corrected (ms)	450 ± 40
QT dispersion (ms)	60 ± 30
QTc dispersion (ms)	90 ± 50
QTc dispersion (%)	
0 to <40 ms	5 (7.0%)
40 to < 90 ms	34 (47.9%)
⩾90	32 (45.1%)
Serum potassium (mEq/l)	4.50 ± 0.84
<3.5 mEq/l	10 (13.0%)
3.5 to <4.0 mEq/l	9 (11.7%)
4.0 to <5.0 mEq/l	39 (50.6%)
5.0 to <6.0 mEq/l	14 (18.2%)
⩾6.0 mEq/l	5 (6.5%)
Serum calcium (mg/dl, adjusted)	9.4 ± 1.2[a]
Serum phosphorus (mg/dl)[b]	5.97 ± 2.7
Serum albumin (g/dl)[c]	3.5 ± 0.50
Hemoglobin (g/dl)[c]	10.9 ± 1.6

b.p.m., beats per minute; LVEF, left ventricular ejection fraction.
[a]To convert to international units (mmol/l), multiply by 0.02495.
[b]To convert to international units (mmol/l), multiply by 0.323.
[c]To convert to international units (g/l), multiply by 10.

Table 2 | Characteristics of the dialysis treatment preceding sudden death

Characteristic	Mean ± s.d. or *n* (%)
Pre-systolic blood pressure (mm Hg)	140.0 ± 26.2
<100	5 (6.6%)
100 to <160	60 (80.2%)
⩾160	11 (13.2%)
Pre-dialysis mean diastolic pressure (mm Hg)	72.8 ± 15.0
Pre-dialysis mean arterial pressure (mm Hg)	95.2 ± 17.2
Post-dialysis systolic blood pressure	127.8 ± 25.9
<100	7 (10.5%)
101–160	54 (80.5%)
⩾160	6 (9.0%)
Post-dialysis diastolic blood pressure (mm Hg)	66.9 ± 15.6
Post-dialysis mean arterial pressure (mm Hg)	86.6 ± 17.4
Mean weight removal (lb)	4.52 ± 2.9
Mean weight removal (%)	2.97 ± 1.88

DISCUSSION

This is the first study in the HD population examining sudden death in which events were classified according to a standard definition and in which complete characterization of each sudden death event was performed. The present study identifies the HD procedure as a major stressor leading to increased sudden death in the 12 h period starting with the dialysis session. The last day of the dialysis-free weekend interval is also associated with a markedly increased rate of sudden death.

The stress resulting in sudden death in the first 12 h period likely derives from the fact that in a very short 4 h period, toxins and fluids that accumulate over 44 or 68 h must be removed. This greatly contrasts with the smooth, continuous clearance provided by the normal kidneys. Unlike the stress from snow shoveling or many other activities known to increase sudden death risk,[4] dialysis occurs repeatedly at regular intervals and is usually not stopped when the patient develops nonspecific symptoms that might precede death.

There was a 1.7 fold increased risk of sudden death events in the 12 h period beginning with the dialysis treatment. Sudden death events were increased both during the dialysis procedure itself and after treatment. Previous studies have noted a number of factors occurring with HD that could lead to cardiac arrhythmias. Potassium fluxes have been associated with an increased incidence of ventricular ectopy,[5] an increased QT interval, and an increased QT dispersion during the HD interval[6–8] – all predictors of sudden death. Patients who died in the first 12 h interval had a lower mean serum potassium level in the prior monthly labs than those dying in the 60–72 h interval, although this did not reach statistical significance – possibly owing to the small sample size. Characterization of sudden death occurring during dialysis has been studied previously. Karnik *et al.*[9] noted that treatment with a 0 mEq/l potassium dialysate was associated with an increased risk of death; a zero potassium dialysate was not available in the outpatient dialysis units in this study, and all patients were maintained on a standard 2.0 mEq/l potassium dialysate.

Ifudu *et al.*[10] have noted a mean pre-dialysis serum potassium of 5.04 ± 0.69 mEq/l (range 3.3–7.4 mEq/l) in a study of 269 stable HD patients compared to a mean serum potassium value of 4.50 ± 0.84 mEq/l in our study. Extremes of serum potassium values are noted in both studies, and both hyper- and hypokalemia are well-known risk factors for sudden cardiac death.[11]

Increased sympathetic activity occurs with HD,[12] and increased sympathetic tone has been associated with mortality and cardiovascular events in the dialysis population.[13] Patients who suffered sudden death in the 0–12 h interval were much less likely to be on beta-blockers than

Table 3 | Characteristics of individuals suffering sudden death according to time interval

Characteristic[a]	0–12 h interval	12–60 h interval	60–72 h interval	*P*-value[b]
Left ventricular ejection fraction (%)	45.4±16.7	46.6±18.0	50.0±16.6	0.55
Congestive heart failure (%)	62.1	56.3	35.3	0.20
Coronary artery disease (%)	55.2	62.5	41.2	0.36
Left ventricular hypertrophy (%)	25.0	40.6	50.0	0.21
Peripheral vascular disease (%)	44.8	46.9	17.7	0.11
Stroke (%)	27.6	28.1	5.6	0.16
Diabetes mellitus (%)	62.1	62.5	35.3	0.14
Frequent non-compliance (%)	17.3	21.9	23.5	0.85
Beta-blocker usage (%)	31.0	37.5	58.8	0.01
Weight gain between treatments	4.5±2.7	4.6±3.2	4.4±2.6	0.99
Serum potassium (mEq/l) in previous month	4.47±0.73	4.30±0.80	4.86±1.0	0.18

[a]For discrete variables, values represent percentage with described condition; for continues variables, values represent mean+s.d.
[b]A χ^2 test was used for the comparison of discrete variables, and analysis of variance testing was performed for continuous variables.

individuals who suffered sudden death in the 60–72 h interval. There are a number of potential reasons for this that will have to be addressed in further studies. Increases in sympathetic activity have been associated with the dialysis treatment,[12,14] and increased sympathetic activity is a well-known risk factor for sudden death.[15] Beta-blockers are believed to prevent ventricular arrythmias in the setting of increased adrenergic stimulation.[16] Alternatively, beta-blockers could be deleterious to patients in the 60–72 h interval. Beta-blockers may lead to increased hyperkalemia,[17] which is more likely to be a problem at the end of the dialysis interval. One study found that predialysis serum potassium was increased by 0.7 mEq/l in HD patients treated for 10 days with propranolol, but was unchanged with treatment with atenolol.[18,19] A third explanation is that there is a treatment indication bias; patients who died in the 60–72 h interval were in general healthier and may have tolerated beta-blockers better and therefore been prescribed them more frequently.

The high prevalence of cardiomyopathy and CAD in our study population provides the perfect setting for arrhythmias to occur. In addition, many patients suffered from an increased QT interval. There was a trend that patients dying in the first time interval to more likely suffer from CHF, CAD, and stroke than those who died in the 60–72 h interval, implying that this interval is more stressful to these individuals than healthier patients.

Once patients survived the acute peri-dialysis period, there was a dramatic decline in the sudden death rate. The sudden death rate then began to rise at the 48–60 h interval. Patients would normally return to dialysis at 48 h in the absence of the weekend interval. In the last 12 h of the weekend interval, sudden death was three times more likely to occur. Increasing volume overload, worsening hypertension, and hyperkalemia all occur before dialysis, and both hypertension and hyperkalemia have been associated with an increased incidence of sudden death.[20,21] Although the weekend interval is highly valued by patients and staff alike, it is associated with a much higher risk of cardiac mortality. The fact that the weekend in general is a time of increased fluid and electrolyte intake likely aggravates this problem. In a prior study, we noted an increased cardiac death rate on Monday for Monday, Wednesday, and Friday HD patients, and on Tuesday for Tuesday, Thursday, and Saturday dialysis patients, but the timing related to the HD session could not be determined.[22] This investigation suggests that the high death rates on Monday and Tuesday are owing to the increased occurrences of death in the 60–72 h interval preceding dialysis; the proportion of deaths occurring in the 12 h interval starting with dialysis were similar, no matter which dialysis treatment of the week was examined.

A weakness of the study was the collection of only a sample of the deaths occurring in the dialysis centers studied. This did not allow for the calculation of incident rates of sudden death. The sample collected was done so without apparent bias, and the clerical personnel collecting the death notification forms were not aware of the purpose of the study.

Sudden death is not the result of dialysis-induced stress producing cardiac arrest in relatively healthy individuals, but rather the stress of dialysis leading to death in those with underlying cardiac disease. Patients who suffered sudden death had a very high prevalence of CHF (55.7%), cardiomyopathy (mean left ventricular ejection fraction 45.7±16.7%), and CAD (55.7%). Diabetes mellitus, CHF, peripheral vascular disease, or CAD was present in 87.5% of cases. These figures are likely to be an underestimate, as undetected CAD or cardiomyopathy may have been present before death. In a prior study of the dialysis centers involved in this study,[23] the prevalence of CHF for the entire dialysis population was 28%, and the prevalence of CAD was 23%. In the United States Renal Data System Dialysis Morbidity and Mortality Wave II Study,[24] a random sampling of dialysis centers in the United States, the prevalence of CHF was 40.8%, and the prevalence of CAD was 37.6%. This study shows that the HD patients suffering from sudden death have underlying cardiac disease. Sudden death did not occur in patients who had normal hearts and perhaps developed hypokalemia or other metabolic abnormalities as a result of dialysis.

The results of this study raise the possibility that additional therapies could be immediately employed in an attempt to reduce the high rates of sudden death observed in

HD patients. Only 40% of patients were taking beta-blockers at the time of death, despite the presence of hypertension in the majority of dialysis patients. Many hypertensive patients were receiving dihydropyridine calcium channel blockers. Other studies have also revealed a decreased rate of beta-blocker usage in dialysis patients.[25] Usage of beta-blockers in patients with CAD or CHF have been associated with a marked decrease in sudden death.[26] A randomized trial of carvedilol recently showed a survival advantage in HD patients with cardiomyopathy.[27] A prospective observational study also suggested a potential benefit of beta-blockers in diabetic dialysis patients.[28]

A recent investigation documented a protective effect of prophylactic defibrillator implantation in patients with non-ischemic dilated cardiomyopathy and a left ventricular ejection fraction less than 35%. One-fourth of the patients who suffered sudden death in this study had an ejection fraction less than 35% and may have benefited from defibrillator implantation.

Another potential therapeutic option is the more frequent adjustment of the dialysis bath in dialysis patients. In all, 24.7% of the patients had a serum potassium value less than 4 mEq/l in the month leading up to sudden death and did not undergo changes in their dialysate bath, with all patients being dialyzed against a standard 2.0 mEq/l potassium bath. Increasing the dialysate potassium would decrease ventricular ectopy and increase the patient's baseline serum potassium levels, which would also decrease the QT interval and QT dispersion during HD – two factors associated with an increased sudden death rate.

A high proportion of deaths occurred during the 4 h dialysis interval, and recent National Kidney Foundation guidelines advocate the presence of defibrillators in all dialysis centers. Defibrillators were present throughout the course of the study in the centers that participated.

Of note, in a recent investigation by Herzog *et al.*,[29] CHF, coupled with hypoalbuminemia and anemia, were associated with a very high annual mortality. A low mean hemoglobin level and low albumin level were noted in our patient population, and correction of these values could potentially improve survival.

Future prospective clinical trials directed at preventing sudden death in dialysis patients should be performed. A recent trial of atorvastatin in HD patients with type II diabetes[30] demonstrated that therapeutic options proven beneficial in the general population may not have similar effects in HD patients.

For many years, nephrologists have concentrated research efforts on perfecting the dialysis technique. However, recent trials have not shown an improvement in patient survival in patients receiving increased dose of dialysis.[31,32] The present study suggests that an increased frequency of dialysis may be beneficial and could potentially prevent sudden death. Whereas daily dialysis might be beneficial, simply increasing treatments to four times per week and avoiding a 3-day dialysis-free interval might have a substantial effect.

It is important to note that despite suffering from cardiovascular disease and renal failure, many of the patients were leading productive lives at the time of their death. Their unexpected death actually provided the motivation to perform this study. Prevention of death in these patients would increase duration of life in many individuals who still have a high quality of life.

MATERIALS AND METHODS

This study was approved by the Wake Forest University School of Medicine Institutional Review Board. A sample of Form HCFA 2746-U3 was obtained from five dialysis centers in the southeastern United States between 1995 and 2003. Owing to changes in the clerical personnel at the dialysis centers over the time course of the study, all death notifications were not forwarded to the investigators. The lapses in collection appeared random in nature. Health Insurance Portability and Accountability Act of 1996 concerns of the participating dialysis centers precluded the retrospective ascertainment of all deaths for these intervals. The participating centers refused to provide information in retrospect on the missing individuals, as it was felt that providing identifying information about these patients would be a breach of confidentiality, despite approval by the Institutional Review Board of Wake Forest University School of Medicine. The dialysis centers participating in the study had survival rates that are similar to national HD patient survival rates. The centers were composed of approximately 50% African-American patients over the time period of the study. End-Stage Renal Disease Death Notification Forms (Form HCFA 2746-U3) were reviewed at approximately annual intervals during the study. Sudden death was defined as unexpected, ans non-traumatic death occurring within 1 h of the onset of symptoms. Patient charts were reviewed, and patients who had other precipitating causes of death (e.g. sepsis, withdrawal from dialysis) were not included. Patients who suffered sudden death after the 72 h interval (owing to missed treatment or other reasons) were not included. Whether patients met sudden death criteria were adjudicated by two of the authors (AJ Bleyer and J Hartman). Deaths during sleep and un-witnessed deaths occurring at home were considered as sudden deaths. Information regarding the sudden death event was obtained from chart review and from interviews with witnesses to the death event. Interviews with witnesses of death events have been helpful in determining sudden death in the investigation of sudden death by Hinkle and Thaler,[33] and also in the Framingham Heart Study.[34] If the death was not witnessed, the time the patient was last seen alive and the time the patient was found dead were recorded.

Demographic data and comorbid conditions were obtained by chart review. CHF was defined as admission for volume overload or a clinical diagnosis of CHF found in the chart. CAD was defined as a history of myocardial infarction, angina, positive stress test, or coronary artery bypass surgery. Peripheral vascular disease was defined as a history of amputation, lower extremity vascular bypass surgery, or intermittent claudication. Cerebrovascular disease was defined as a history of stroke, transient ischemic attack, or carotid endarterectomy. Non-compliance was defined as a history of missed treatments, markedly excessive fluid gains, or marked, willful non-compliance with medications. Data were obtained from the patient's most recent echocardiogram and electrocardiogram. The QT interval was calculated as the mean QT interval obtained from 12 different leads on the electrocardiogram using Bazett's formula

(QTc). The serum potassium and calcium values were obtained from the patient's most recent monthly laboratory values, and from the month prior. The serum calcium was adjusted for serum albumin as described previously.[35]

The timing of sudden death was determined as the time from the start of dialysis until the time of death. If the exact time of death was not known, the probability of death was evenly distributed from the time the patient was last seen alive to the time the patient was found dead. For instance, if the patient was last seen alive 6 h after dialysis and was found dead 8 h after dialysis, a value of 0.5 was given for the hour between 6 and 7 h, and 0.5 for the hour between 7 and 8 h. We hypothesized that a higher proportion of sudden deaths would occur in the 12 h interval beginning with the start of dialysis and in the 12 h interval occurring from 60 to 72 h after the start of dialysis. This latter interval occurs once during the week – occurring at the end of the weekend interval. The relative risk is calculated as the proportion of observed deaths in the 12 h interval vs the expected number of deaths, assuming that the occurrence of death would be evenly distributed over time. As Figure 1 demonstrates, the 48–60 h and the 60–72 h interval occur only one time during the week, as compared to three times per week for each of the other time intervals. Therefore, one would expect one-third as many deaths in these two later intervals. A χ^2 test was performed to determine significance.

Statistical analysis was performed by Gregory Russell, PhD, Anthony Bleyer, MD, and Joel Hartmann, MD. Descriptive statistics, including means, s.d.'s, and ranges for continuous measures and frequencies and proportions for categorical data, were calculated. χ^2 tests were used to test for differences between observed and expected frequencies in day and timing of deaths of patients. For other categorical measures, χ^2 tests were used to test for association between outcome measures and day/time of death.

ACKNOWLEDGMENTS

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